Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 124-126 and 129-131 are pending in this application and are rejected on various grounds. Claims 127 has been canceled without prejudice or disclaimer. The functional recitation of Claim 124 has been amended to recite that the nucleic acid encoding said polypeptide is amplified in "lung carcinomas" support for which is found in Table 8, page 546 of the specification. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, First paragraph

Claims 124-127 and 129-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." Claims 124-127 and 129-131 are rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would clearly not know how to use the claimed invention."

In response to Applicants' previous assertions, the Examiner contends that "no evidence has been submitted that it is the norm rather than the exception that protein levels are increased when gene amplification occurs in cancer". The Examiner asserts based on Pennica *et al.* that there is not always a correlation (between DNA and protein levels) and thus contends that the skilled artisan would have to perform experiments to verify it. Further, the Examiner quotes two references, Konopka and Haynes, to show that "DNA amplification is not always associated with overexpression of the gene product." Thus, the Examiner contends that the proposed use for the PRO341 polypeptide are simply starting points for further research and investigation into potential practical used of the proteins and antibodies. Applicants respectfully traverse these rejections.

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.**

Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

A *prima facie* case of lack of utility has not been established

Applicants have asserted utility for PRO341 polypeptides based on gene amplification of the DNA encoding polypeptide PRO341 in lung carcinomas.

The Examiner bases the assertion, that increases in gene copy number do not reliably correlate with increased gene expression or polypeptide expression, on exemplary literature reports like Pennica *et al.*, Konopka *et al.*, and Haynes *et al.*, and concludes that the PRO 341 polypeptides lack utility.

In the previous Office action, the Examiner had asserted that Pennica *et al.* teaches that "*WISP*-2 DNA was amplified in colon cancer cell lines and in human colon tumors, but RNA expression was reduced (2- to >30-fold) in 79% of the tumors. This evidence indicates that DNA amplification is not always associated with overexpression of the gene product." However, the Examiner has not mentioned Pennica's results for the *WISP*-1 gene. Applicants draw attention to Pennica's showing that **a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene"in 84% of the tumors examined**. Thus, while Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches a correlation for the *WISP*-1 gene. Further, while Pennica's teachings are specific for the *WISP* family of genes, Pennica teaches nothing regarding such a lack of correlation in genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica teaches nothing of the correlation between gene amplification and polypeptide over-expression in general.

Further, the Examiner cites the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to the amplification of the *abl* gene . . . ." Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka does not disclose any generalized teaching about the

correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone. Thus, the combined teachings of Pennica and Konopka are not directed towards genes in general, but to single genes or genes within a family and thus, their teachings have been misinterpreted in this rejection.

The Examiner further says that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." In fact, very <u>few</u> data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Haynes *et al.*

<u>It is "more likely than not" for amplified genes to have increased mRNA and protein levels</u>

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, just as in Haynes, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Ornfoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Ornfoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1,

abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack *et al.,* (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that gene amplification correspondingly increases mRNA expression, in general.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed

this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm (as in Pennica or Konopka) which are exceptions rather than the rule, in the vast majority of amplified genes, the combined teachings in the art exemplified by Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, and the Polakis declaration overwhelmingly teach that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO 341 gene, that the PRO 341 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO 341 proteins also has utility in the diagnosis of cancer and thus, one of skill in the art would know exactly how to use these molecules.

Claimed proteins would have diagnostic utility even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO 341, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants once again refer to the Declaration by Avi Ashkenazi, Ph.D., which explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO 341 polypeptide, for example, in detecting over-expression or absence of expression of PRO 341. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides for the diagnosis of lung carcinoma. Accordingly, Applicants request that the present rejection to the present claims be reconsidered and withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 124-127 and 129-131 were rejected under 35 U.S.C. §112, second paragraph for being indefinitefor reiciting the term "the extracellular domain."

Without acquiescing to the propriety of this rejection, Applicants have canceled references to "the extracellular domain" and "the extracellular domain....lacking its associated signal sequence" in the pending claims. Accordingly, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 7, 2004

Daphne Reddy

Daphne Reddy
Reg. No. 53,507

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638
2045839